Application is submitted herewith as Attachment F.

The Assistant Commissioner for Patents is hereby authorized to charge any and all fees due which may be required by this paper, including any extension of time fees, to Account No. 10-0447/32892.00002.

Remarks

In response to the Amendment After Final mailed on August 26, 1998, copies of two different 37 C.F.R. §131 declarations previously filed in this application, which were executed by Mr. Dave Bova, the named inventor, as Attachments A and B, are submitted herewith. The substance of these 37 C.F.R. §131 declarations satisfy the requirements of 37 C.F.R. §1.608(b). Therefore, to avoid duplication, no additional declaration by the inventor, David Bova, is submitted at this time. Also submitted herewith is a 37 C.F.R. §1.608(b) declaration executed by George M. Toth, which corroborates David Bova's 37 C.F.R. §131 declarations, dated March 27, 1996 and August 17, 1995, respectively (See Attachment D).

I. The Final Office Action, August 26, 1998

1.) In the August 26, 1999 final office action, the Examiner has rejected previous claims 1-9 and 15-18 under 35 U.S.C. §102(e) as being anticipated by O'Neill et al., U.S. patent No. 5,208,181 (hereinafter the "O'Neill Patent").

2.) As to the §102(e) rejection, the Examiner has adopted the position in the August 26, 1998 Final Office Action that the O'Neill Patent ***specification*** teaches the claimed methods and relies upon O'Neill Patent claims 1-11, and the O'Neill Patent specification at col. 2, lines 35 *et seq.*, col. 3, lines 30-65 and 67, and col. 4 for support. The Examiner therefore concludes that the O'Neill Patent cannot be overcome by a 37 C.F.R. §131 declaration. Rather, according to the Examiner, such rejection can be overcome ***only*** by an interference proceeding.

Further consideration of this application for U.S. patent, in view of the following remarks and submitted declarations, is respectfully requested.

II. Related Applications

The above-identified application for U.S. patent is a continuation-in-part of U.S. Patent Application, Serial No. 08/124,392, filed on September 20, 1993 (the "Parent Application")(See

Attachment F).

III. Background

Nicotinic acid has been used for many years in the treatment of hyperlipidemia. As further pointed out, this drug has long been known to exhibit the beneficial effects of reducing total cholesterol, low density lipoproteins or "LDL cholesterol", triglycerides and apolipoprotein a (Lp(a)) in a hyperlipidemic, while increasing desirable high density lipoproteins or "HDL cholesterol".

Generally speaking, nicotinic acid, when in immediate release or crystalline form, is normally administered three times per day after meals. While this dosing regimen is known to provide beneficial effect on blood lipids, it is not without a draw back. The major side effect of immediate release or crystalline nicotinic acid is cutaneous flushing, which has discouraged widespread use of the immediate release forms of nicotinic acid for treatment of hyperlipidemia.

In order to avoid or reduce cutaneous flushing, certain compounds have been suggested for co-administration with an effective antihyperlipidemic amount of immediate release nicotinic acid, which include guar gum or inorganic magnesium salts.

Another alternative developed to avoid or reduce the cutaneous flushing side effects associated with immediate release nicotinic acid is the use of sustained release nicotinic acid formulations. The sustained release nicotinic acid formulations have been designed to slowly release the nicotinic acid from the solid oral dosage forms, such as tablets or caplets. The nicotinic acid release reduces and prolongs blood levels of the drug and thus minimizes the cutaneous flushing side effect commonly associated with immediate release forms of nicotinic acid.

While the sustained release formulations have minimized the cutaneous flushing side effects of the immediate release forms of nicotinic acid, the sustained release formulations present other disadvantages. Numerous studies in hyperlipidemics have been conducted with a number of sustained release nicotinic products. These studies have reported that the sustained release nicotinic acid products do ***NOT*** have the same advantageous lipid altering effects as immediate release nicotinic acid products and, in fact, ***often have a worse side-effect profile compared to the immediate release nicotinic acid products***. The major side-effect noted with sustained release nicotinic acid formulations are that they cause greater incidences of liver toxicity, i.e., hepatotoxicity.

In fact, certain investigators have concluded that the sustained release forms of nicotinic acid "should be restricted from use" due to the serious nature of the liver toxicity caused by the sustained release nicotinic acid formulations.

Because of the side-effects associated with the immediate release forms of nicotinic acid, i.e., cutaneous flushing, and with the sustained release forms of nicotinic acid, i.e., liver toxicity, nicotinic acid has experienced less than optimum utilization in the treatment of hyperlipidemia.

Therefore, it can be appreciated that there is a need for a nicotinic acid treatment which would provide hyperlipidemics with effective reductions in serum lipids without necessarily inducing cutaneous flushing while providing an acceptable safety profile, especially with regard to liver toxicity.

IV. The Claimed Invention

The present invention overcomes the disadvantages and drawbacks discussed above which are associated with nicotinic acid therapy available heretofore through the discovery of a novel method useful for treating hyperlipidemia in a patient.

Generally Speaking, method claims 1-9 and 15-18 involve orally dosing a patient with an effective antihyperlipidemia amount of nicotinic acid only once per day during the evening or at night as a single dose of a sustained release nicotinic acid dosage form comprising nicotinic acid and at least one pharmaceutically acceptable carrier to effectively lower a serum lipid.

Thus, these unique methods of the present invention, as claimed, make it possible to deliver an effective antihyperlipidemia amount of nicotinic acid via a sustained release preparation without causing drug-induced, treatment-limiting side effects, such as hepatotoxicity and/or elevations in uric acid and/or glucose levels, commonly associated with sustained release nicotinic acid therapy utilized heretofore.

V. FDA Approval

It has been respectfully point out that the FDA has recently substantiated the significance of Applicant's invention. In July, 1997, the FDA approved Applicant's use of a sustained release nicotinic acid product to treat mixed dyslipidemia in patients without causing drug-induced side effects, e.g., hepatotoxicity. This is the **FIRST** extended release nicotinic acid product to have been

approved by the FDA as being both safe, i.e., without side-effects, and effective, i.e., providing a meaningful therapeutic improvement. The FDA's Notice of Approval, for Kos Pharmaceutical, Inc.'s sustained release nicotinic acid product, is submitted herewith as Attachment E.

VI. The O'Neill Patent

The O'Neill Patent is a continuation-in-part of Evenstad *et al.,* U.S. patent No. 5,126,145, which was issued on June 30, 1992 and filed on June 11, 1990 (hereinafter "Evenstad Patent"). The O'Neill Patent was filed on June 29, 1992 and was issued on December 7, 1993. According to Dr. Raines Declaration, dated May 22, 1996, which has been previously submitted in this application for U.S. Patent, of which a copy thereof is submitted herewith as Attachment C, the Evenstad Patent does not teach or even suggest the O'Neill claimed methods of administering niacin at a time of day targeted to coincide with the time at which cholesterol is maximally synthesized in the human liver. Also according to Dr. Raines, the once daily, diurnal variation-related dose of niacin described by O'Neill cannot be said to follow from the two dose, diurnal variation unrelated regimen of the Evenstad Patent. See ¶6, Dr. Raines Declaration, Attachment C.

In view of the fact that the Evenstad Patent provides no support for the subject matter described and claimed in the O'Neill Patent, it is respectfully submitted that the O'Neill Patent is entitled to only June 29, 1992, the actual filing date of the O'Neill Patent as its earliest priority date, and not the earlier Evenstad Patent filing date of June 11, 1990.

VII. The Invention Defined by Claims 1-9 and 16-18 of the Present Application and the Invention Defined by the Claims of the O'Neill Patent are Patentably Distinct

37 C.F.R. governs the procedure in patent interferences in the U.S. Patent and Trademark Office. According to 37 C.F.R. §1.601(I):

> An interference is a proceeding instituted in the Patent and Trademark Office before the Board to determine any question of patentability and priority of invention between two or more parties claiming the same patentable invention.

Applicant respectfully submits that an interference based upon independent claim 1 of the O'Neill Patent is improper because the above-identified application for U.S. patent does not have

support for the composition limitations recited in main claim 1 of the O'Neill Patent and such composition limitations in main claim 1 of the O'Neill Patent were critical to the patentability of all claims in the O'Neill Patent.

Applicant further respectfully submits that any interference based upon pending independent claims 1 or 15 of the above-identified application for U.S. patent is only proper to determine priority as to the above-identified application for U.S. patent, not the O'Neill Patent, in view of the fact that all claims in the O'Neill Patent are formulation specific, and such composition limitations in those issued claims were critical to their patentability.

A.) O'Neill *et al.* Material Limitations

More specifically, the O'Neill Patent claims are based on the use of a **single daily dose of a defined nicotinic acid composition which may or may not induce hepatotoxicity.** More specifically, the O'Neill Patent claims claim a method *consisting essentially* of administering a single daily dose of a niacin composition that comprises: (1) "about 5-30% high viscosity hydroxypropylmethylcellulose having a nominal viscosity, 2% aqueous solution, of at least about 10,000 cps, a methoxyl content of about 7-20%," (2) "about 2-15% of a water-soluble pharmaceutical binder," (3) "about 2-20% of a hydrophobic component," and (4) "about 30-90% niacin." See claim 1 in the O'Neill Patent, which is submitted as Exhibit I. That is, the broadest claim of the O'Neill Patent which is directed to a method that requires the administration of a single *daily* dose of a *defined niacin composition*. Dependent claim 3 in the O'Neill patent, however, limits the time of administration to "with the evening meal...or after the evening meal....but before bedtime".

B.) Application Material Limitations

In contrast, currently pending claims 1-9 and 15-18 in the above-identified application for U.S. patent are directed to a method of treatment comprising (1) the administration of "nicotinic acid once per day only during the evening or at night," and (2) wherein the "nicotinic acid is an oral sustained release solid dosage form." In other words, currently pending independent method claims 1 and 15 are generic; they are not formulation specific like all issued claims in the O'Neill Patent. Thus, currently pending independent method claims 1 and 15 are not formulation limited, so long

as the composition is an oral sustained release solid dosage form which, when administered, delivers an effective amount of nicotinic acid.

C.) Patentably Distinct Inventions

The difference between the presently claimed method and the O'Neill method are due to the fact that the present inventor discovered that hyperlipidemia can be effectively treated with an oral sustained release nicotinic acid solid dosage form when it is administered only as a single effective dose during the evening or at night. In contrast, the methods claimed by the O'Neill Patent are dependent upon the use of a defined or specific niacin composition administered once a day (with the evening meal or after the evening meal but before bedtime - (claim 3).

Applicant respectfully emphasizes that the O'Neill method claims rely on the use of a particular or specific nicotinic acid formulation, and that the composition limitations recited in the O'Neill Patent claims **were critical** to a determination of patentability, as shown by the file history. First, the original O'Neill Patent application claims were broader than the issued claims. Still, the original claims required the use of a particular or specific nicotinic acid composition defined as an admixture of "about 5-30 % high viscosity hydroxypropyl cellulose, about 2-15% of a water-soluble pharmaceutical binder, about 2-20% of a hydrophobic component and about 30-90% niacin." See original claim 1 of the O'Neill Patent application. Apparently, O'Neill *et al.* believed that the efficacy of the "daily dose" of nicotinic acid was dependant upon **the particular formulation.**

Second, the Examiner of the O'Neill Patent took the position that the particular "sustained release components appear critical to the invention."[1] The Examiner withdrew this basis for rejection after O'Neill *et al.* added a further limitation to claim 1 that defined the nature of the hydroxypropyl methylcellulose component. This action reinforces the proposition that the nature of the composition was critical to the once-a-day dosing regimen.

Third, the O'Neill Patent Examiner also rejected the claims on the basis of a lack of enablement because "[c]laim language reciting consisting essentially of administering the particular

[1]Office Action of October 26, 1992, at page 2.

admixture is considered necessary for proper enablement."[2] The Examiner later withdrew this basis for rejection after O'Neill *et al.* added the language "consisting essentially of" to claim 1. Again, this additional limitation emphasizes the requirement of the O'Neill niacin composition to perform the claimed method.

In short, the presently claimed inventions are based upon treating hyperlipidemia with an oral sustained release nicotinic acid solid dosage form, while the O'Neill method claims are based upon the use of a defined or specific nicotinic acid composition. Applicant respectfully asserts, therefore, that the two inventions are patentably distinct, contrary to the requirement for interference provided by 37 C.F.R. §1.601(j).

VI. An Interference Based Upon Independent Claim 1 in the O'Neill Patent is Improper - Such an Interference Would Clearly Violate M.P.E.P. §2301.01

According to M.P.E.P. §2301.01 (Preliminaries to an Interference), it clearly states:

> (b) Express limitations in the claim should not be ignored ***nor should limitations be read therein***. (Emphasis added)
>
> (f) ***If doubt exists as to whether there is an interference, an interference should not be declared.*** (Emphasis Added)

The M.P.E.P. §2301.01 makes clear that an express limitation found in an issued claim can ***not*** be ignored. Moreover, M.P.E.P. §2301.01 makes clear that limitations cannot be read into claims. Thus, it is respectfully submitted that an interference proceeding based upon independent claim 1 of the O'Neill Patent will be improper if any limitation in independent claim 1 of the O'Neill Patent is ignored or if support for all composition limitations or properties recited in main claim 1 of the O'Neill Patent cannot be found in the above-identified application for U.S. patent. In other words, it is improper for the Examiner to ignore any limitations of independent claim 1 of the O'Neill Patent or to read any limitations of independent claim 1 of the O'Neill Patent into any pending claim 1-9 and 15-18 of the above-identified application for U.S. patent for purposes of provoking an interference.

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[2]Office Action of March 31, 1993, at page 2.

A.) The O'Neill Patent Material Limitations

As discussed above, the O'Neill Patent is based on the use of a **single daily dose of a defined nicotinic acid composition.** The O'Neill Patent claims are clearly limited to lowering serum lipids or a lipid component based upon the use of a single daily dose of ***a specific nicotinic acid composition.*** Because the O'Neill Patent was issued on Dec. 7, 1993, which is more than two years ago, the issued formulation specific claims in the O'Neill Patent cannot be broadened by reissue nor by an interference proceeding.

B.) The Specification of the Above-Identified Application for U.S. Patent Does Not Have Support for All Limitations Found in Independent Claim 1 in the O'Neill Patent

By way of example, the specification of the above-identified application for U.S. patent does not teach or suggest the particular hydroxypropylmethylcellulose claimed by independent claim 1 of the O'Neill Patent. Nor does the specification of the above-identified application for U.S. patent teach or suggest the "hydrophobic component" as claimed in independent claim 1 of the O'Neill Patent.

C.) It is Clear that an Interference Based upon Independent Claim 1 of the O'Neill Patent Is Improper

Thus, because of the composition limitations in independent claim 1 of the O'Neill Patent were critical to the patentability of all claims in the O'Neill Patent under 35 U.S.C. §112 and the issued claims in the O'Neill Patent cannot be broadened, such composition limitations cannot be ignored. Moreover, because the specification of the above-identified application for U.S. patent does not disclose or suggest such composition limitations, they cannot be read into pending claims 1-9 and 15-18 of the above-identified application for U.S. patent. In addition, because the specification of the above-identified application for U.S. patent does not disclose or suggest such composition limitations, a count could not be drafted which includes such composition limitation. It is therefore respectfully submitted that if an interference is declared based upon main claim 1 of the O'Neill Patent, such interference would be improper because it would clearly violate M.P.E.P. §2301.01.

VIII. An Interference Based Upon Pending Claims 1 and/or 15 of the Above-Identified Application for U.S. Patent may only Determine whether the Above-Identified Application for U.S. Patent has Priority to Generic Claims 1 and 15, not whether the O'Neill Patent has Priority for Such Generic Claims

A.) The O'Neill Patent Claims 1- 10 Cannot Claim Priority to the Filing Date of the Evenstad Patent, i.e., June 11, 1990

As discussed above, the Evenstad Patent does not provide support for the O'Neill Patent claims. See Dr. Raines' Declaration submitted herewith (Attachment C). Thus, The O'Neill patent claims are limited to the filing date of the O'Neill Patent, i.e., June 29, 1992. Moreover, the claims in the O'Neill Patent are not generic, they are formulation specific, and they cannot be broadened by reissue or by an interference in view of the fact that the O'Neill Patent was issued on Dec. 7, 1993, more than two years ago.

B.) The Inventions Claimed in all Presently Pending Claims 1-9 and 15-18 were Conceived and Reduced to Practice in the United States Prior to June 29, 1992

Copies of Dave Bova's Declarations, Attachments A and B, clearly show that all presently pending claims were conceived and reduced to practice in the United States prior to June 29, 1992, the earliest priority date for all claims issued in the O'Neill Patent. According to Dave Bova, the inventor, the claimed invention was utilized in a study conducted in the United States which began in 1990 and ended on March 20, 1991, and the first patient was enrolled in the study on June 11, 1990. See Attachments A and B. The testimony declared by Dave Bova in his declarations, Attachments A and B submitted herewith, has been corroborated by George M. Toth in his 37 CFR §1.608(b) declaration submitted herewith. Moreover, support for such study attested to by Dave Bova in Attachments A and B is reported in Tables I-VII in both the above-identified application for U.S. patent and the Parent Application to which the above-identified application for U.S. patent relates (See Exhibit F). It is therefore respectfully submitted that the above-identified application for U.S. patent is entitled to the filing date of the Parent Application, i.e., September 20, 1993, as its effective filing date. It is further respectfully submitted that the inventions, as described and

claimed in claims 1-9 and 15-18 in the above-identified application for U.S. patent, were conceived and reduced to practice in the United States prior to June 29, 1992. It is further respectfully submitted that any interference based upon main claims 1 and 15 of the above-identified application for U.S. patent is proper for the purposes of only determining whether Applicant has priority as to such generic claims 1 and 15, not whether the O'Neill Patent has priority over Applicant as to such generic claims, in view of the material composition limitations introduced into all claims of the O'Neill Patent and the fact that the O'Neill Patent was issued more than two years ago. It is further respectfully submitted that to the extent an interference is proper between the above-identified application for U.S. patent and the O'Neill Patent, Applicant is *prima facie* entitled to judgement and priority in view of the fact that the O'Neill Patent is limited to June 29, 1992 as its earliest priority date, and the first patient in such study was enrolled on June 11, 1990, the very same day that the Evenstad Patent was filed.

An affidavit by David Bova under 37 C.F.R. §1.608(b) has not been submitted with this Amendment After Final to avoid duplication. In summary, it is respectfully submitted that: (1) this Amendment After Final is fully responsive to the Final Office Action dated August 26, 1998 without the submission of an affidavit under 37 C.F.R. §1.608(b) by the inventor David Bova in view of his earlier filed declarations in this application for U.S. patent; (2) the O'Neill Patent is limited to its filing date of June 29, 1992; (3) the issued claims in the O'Neill Patent cannot be broadened; (4) an interference based upon main claim 1 of the O'Neill patent is improper for the reasons discussed above; (5) an interference based upon main claims 1 and 15 of the above-identified application for U.S. patent is proper for the purposes of only determining whether the applicant has priority as to generic claims 1 and 15, not whether the O'Neill Patent has priority over applicant to such generic claims, in view of the material composition limitations introduced into all claims of the O'Neill Patent and the fact that the claims in the O'Neill Patent are formulation specific and they cannot be broadened; (6) the inventions as described and claimed in claims 1-9 and 15-18 in the above-identified application for U.S. patent were conceived and reduced to practice in the United States prior to June 29, 1992; and (7) Applicant is *prima facie* entitled to judgement and priority in view of the fact that the O'Neill Patent is limited to June 29, 1992 as its earliest priority date.

However, if, after review of the declarations submitted herewith, the Examiner is of the position that an additional declaration is needed, applicant respectfully requests that the Examiner so advise.

IX. According to M.P.E.P. §2301.01, if Doubt Exists as to Whether an Interference Exists, an Interference Should Not be Declared

In the event that the Examiner is uncertain that an interference should be declared, M.P.E.P. §2301.01 mandates that an interference **SHOULD NOT** be declared. Specifically, M.P.E.P. §2301.01 states:

> In determining whether an interference is necessary, a claim should be given the broadest interpretation which it reasonably will support bearing in mind the following:
>
> (f) If doubt exists as to whether there is an interference, **an interference should not be declared.**
> (emphasis added)

It is therefore respectfully submitted that the foregoing is a sufficient basis by itself for not declaring an interference or, at the very least, for creating doubt as to whether there is an interference.

Even if the Examiner is of the opinion that none of the foregoing is established, should the Examiner be uncertain as to any of these points or any other points concerning whether an interference exists, then it is respectfully submitted that doubt exists so that M.P.E.P. §2301.01 controls and, therefore, mandates that an interference should not be declared.

X. Conclusion

To the extent any fees are due, including extension of time fees, as a result of the presentation hereof, for which payment has not been made, the Assistant Commissioner for Patents is hereby authorized to charge such fees to our Deposit Account No. 10-0447/32892.00002.

It is respectfully submitted that all presently pending claims are patentably distinct over the disclosures of record when the disclosures are considered either alone or any appropriate combination. It is further respectfully submitted that all currently pending claims are in conformance

with 35 U.S.C. §112. As a result of the foregoing amendments and remarks together with the accompanying documents, the present application is now in condition for allowance, or at the very least, in condition for an interference having counts based upon claims 1 and 15 of the above-identified application for U.S. patent. Therefore, it is earnestly solicited that either an interference having counts based upon claims 1 and 15 of the above-identified application for U.S. patent be declared or early passage of the above-reference application for U.S. patent to issuance be granted.

Should the Examiner have any questions or require additional information or clarification, Applicant requests that the Examiner contact the attorney of record herein, Peter J. Manso, at the phone numbers noted below.

Respectfully Submitted,

Date: February 26, 1999

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